IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Luo *et al.*

Application No.: 09/420,092

Filed: October 18, 1999

For: CELL CYCLE PROTEINS ASSOCIATED WITH PCNA, COMPOSITIONS AND METHODS OF USE

Examiner: Michele Flood

Art Unit: 1654

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DECLARATION UNDER 37 C.F.R § 1.132 OF DR. YASUMICHI HITOSHI

MCFlood
9/29/03

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

I, Yasumichi Hitoshi, M.D., Ph.D., being duly warned that willful false statements and the like are punishable by fine or imprisonment or both (18 U.S.C. § 1001), and may jeopardize the validity of the patent application or any patent issuing thereon, state and declare as follows:

1. All statements herein made of my own knowledge are true, and statements made on information or belief are believed to be true and correct.

2. I received my medical degree from Kumamoto University Medical School in 1987. I received a Ph.D. in immunology from The Institute for Medical Immunology, Kumamoto University Medical School in 1991. I was a postgraduate research associate at the Institute for Medical Immunology, Kumamoto University Medical School in 1991 and at the Institute of Medical Science, The University of Tokyo from 1992-1995. From 1995-1998 I was a postdoctoral fellow in the Department of Molecular Pharmacology at Stanford University. A copy of my curriculum vitae is attached hereto as Exhibit C.

3. I have worked in the department of Cell Biology at Rigel Pharmaceuticals, Inc. since 1998. Currently, I am Associate Director and Project Leader at Rigel Pharmaceuticals, Inc.

4. The present invention claims methods to identify bioactive agents that bind to R0101, a cell cycle protein that is associated with certain cancers.

5. I have read and am familiar with the contents of the patent application. In addition, I have read the Office Action, mailed December 18, 2002, received in the present case. It is my understanding that the Examiner believes that the present invention does not provide a "real world" use for the claimed method. This declaration is provided to demonstrate that the description of cell cycle protein R0101 in the specification teaches to a scientist, such as myself, that this protein has uses in the field beyond experimentation to identify it activity and that identification of bioactive agents that bind to cell cycle protein R0101 has real world utility.

6. R0101 is a cell cycle protein that has increased expression in certain cancers and is thus associated with certain cancers, *e.g.*, esophageal cancer, breast cancer, uterine cancer, cervical cancer, brain cancer, kidney cancer, and lung cancer. Because of the overexpression of R0101 in certain cancers, one of skill in the art would recognize that R0101 is a useful protein and that bioactive agents that bind to R0101 are also useful. For example, one of skill in the art would expect that bioactive agents that bind to a protein known to be overexpressed in certain cancers, as is R0101, would be useful as indicators of expression of the R0101 and therefore as a diagnostic or prognostic indicators of certain cancers.

7. R0101 is a cell cycle protein that has increased expression in certain cancers and is thus associated with the disease cancer. Figure 5 of the application shows that R0101 exhibits elevated expression in certain cancers relative to non-cancer cells from the same tissues , *e.g.*, esophageal cancer, breast cancer, uterine cancer, cervical cancer, brain cancer, kidney cancer, and lung cancer. It is well-known that

proteins that are overexpressed in cancer cells can be used in diagnostic or prognostic evaluation of the disease.

8. The specification provides ample evidence to conclude that PCNA protein, a protein with a recognized role in DNA synthesis (discussed below), is a ligand for cell cycle protein R0101. Figure 6 shows that R0101 binds to PCNA in cells and moreover, that R0101 competes with p21 for binding to PCNA. P21 is another protein with a recognized role in the cell cycle and an association with certain cancers. R0101 binding to PCNA occurs through a conserved PCNA binding domain. (See, *e.g.*, figure 2b, p15PAF and R0101 are used interchangeably and refer to the same protein.) In addition, the R0101 binding to PCNA is specific and can be eliminated by specific mutations of the R0101 protein. (See, *e.g.*, Figure 7.) These R0101 ligand binding activities demonstrate the physiological role of cell cycle protein R0101.

9. Because of the overexpression of R0101 in certain cancers, one of skill in the art would recognize R0101 as a useful protein. For example, one of skill in the art would expect that a protein known to be overexpressed in certain cancers, as is R0101, would be useful as a diagnostic or prognostic indicator of those cancers.

10. Because of the overexpression of R0101 in certain cancers, one of skill in the art would recognize that bioactive agents that bind to R0101 are useful. For example, one of skill in the art would expect that bioactive agents that bind to a protein known to be overexpressed in certain cancers, as is R0101, would be useful as indicators of expression of the R0101 and therefore as a diagnostic or prognostic indicators of certain cancers.

11. After reading the present application, the skilled practitioner would know how to identify bioactive agents that bind to R0101. Methods to determine molecules that bind to a protein are known to those of skill in the art. Applicants have isolated a nucleic acid that encodes the R0101 protein and provide both the nucleic acid (*i.e.*, SEQ ID NO:1) and the encoded amino acid (*i.e.*, SEQ ID NO:2.) Applicants also

provide description of bioactive agents at page 23, line 33 through page 27, line 26. Applicants further provide methods determine binding to R0101 and to screen for bioactive agents that bind to R0101 at page 27, line 31 through page 31, line 32.

12. There are many instances where binding of an agent to a particular protein is useful for diagnosis, or determination of prognosis, even though the protein itself may not cause cancer. Bioactive agents that bind to proteins that are overexpressed in certain cancers can be used to diagnose the cancer or provide prognostic information about the disease, without a direct connection to the cause of the disease. For example, p21, a tumor suppressor, is over expressed in some esophageal cancers and serves as a prognostic indicator of increased patient survival. (See Natsugoe *et al.*, *Clinical Cancer Research*, 5:2445-2449 (September, 1999), attached as Exhibit B). Also, prostate specific antigen (PSA) serves as a useful diagnostic indicator for prostate cancer, even though a direct causal relationship between expression of the protein and the disease has not been shown. Thus, providing a prognostic or diagnostic test for a particular cancer is useful, even if the original cause of the cancer is unrelated to the protein targeted for diagnostic or prognostic information. Similarly, it is perfectly reasonable to expect that the identification of bioactive agents that bind to R0101, a cell cycle protein that is highly expressed in some cancers, is an appropriate strategy to identify specific diagnostic or prognostic tools for certain cancers.

13. In view of the foregoing, it is my scientific opinion that one of skill in the art, at the time the application was filed, would recognize the real world utility of the nucleic acids of the present invention.

Date: 3/18/03 By: _____

Yasumichi Hitoshi, M.D., Ph.D.